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Original Research

Treatment of Recurrent Granulosa Cell Tumors of the Ovaries: Single-center Experience

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Abstract

Objectives: Granulosa cell tumors (GCTs) are rare ovarian tumors with a high rate of late recurrence, which can present a significant challenge for surgical management. This study aims to evaluate the outcomes of debulking surgery for recurrent GCTs that involve major abdominal vessels and the liver.

Methods: We present a retrospective case series of three patients with recurrent GCTs who were treated at our reference center between 2024 and 2025. We collected data on patient demographics, medical history, recurrence location, treatment details, and follow-up. All data are presented descriptively.

Results: The patients' ages ranged from 53 to 70 years. The time from initial surgery to the first recurrence ranged from 6 to 26 years. Two patients experienced extra-pelvic recurrences in the retroperitoneal space, while one had a pelvic recurrence. All three patients underwent debulking surgery, with two patients experiencing second recurrences and one patient experiencing a third. One patient required anterior wall resection and reconstruction of the Inferior Vena Cava (VCI). Notably, two patients had elevated levels of CEA and CA-125 that peaked before recurrence.

Conclusion: Our findings suggest that the number of GCT recurrences is not as critical as the ability to perform a complete, safe resection. Surgery alone, with a focus on radical resection of recurrent foci, appears to be the primary determinant of favorable patient survival, even when it involves complex procedures like oncovascular resection. Repeated resections, even for multiple recurrences, can lead to favorable long-term outcomes.

Keywords: Granulosa Cell Tumors, Recurrent Ovarian Cancer, Radical Surgery, Repeated Resections

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Granulosa cell tumors (GCTs) originate from the granulosa cells of the sex cords, which are responsible for producing sex steroids and peptides essential for folliculogenesis.[1] GCTs are a rare type of ovarian tumor, constituting less than 5% of all cases. They are classified into two main types: adult GCT and juvenile GCT.[1]

Adult GCT is the more common form, making up 95% of cases, and typically affects perimenopausal women in their fifth decade. Juvenile GCT is rare and is more commonly diagnosed in premenarchal females.[1] A key characteristic of these tumors is their early-stage presentation, often accompanied by symptoms of hyperestrogenism. The prog-

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nosis for GCTs is generally better than for other epithelial ovarian tumors, especially when treated with radical surgery, which can be curative.[2]

The development of GCTs involves an accumulation of genetic and epigenetic changes. Genetic aberrations have been noted on chromosomes 1, 3, 6, 11, 12, 15, 17, and X, along with chromosomal microsatellite instability and loss of heterozygosity.[3] Epigenetic changes, such as hypermethylation, have also been reported in various gene loci, including p16, estrogen receptor-α (ER-α), BRCA1, and others.[3] The inherited component of GCT is suggested by its association with conditions like Peutz-Jeghers and Potters syndromes, and in the case of juvenile GCT, with Ollier and Maffucci diseases.[3]

GCTs are typically slow-growing tumors that often present cystic and hemorrhagic components.[1] Common symptoms include palpable mass and hyperestrogenism-related symptoms.[4, 5] Several factors influence prognosis, including patient age, tumor size, rupture, mitotic index (Ki-67), nuclear atypia, aneuploidy, and p53 overexpression.[1, 6] The primary surgical treatment for GCTs with a high probability of survival is surgical debulking combined with the excision of metastatic lymph nodes.[7]

Unfortunately, GCT recurrence is often insidious and can occur decades after initial treatment. More than 20% of stage I GCTs will recur within 5-10 years post-surgery.[8-11] A study by Lee et al. reported an 8 out of 38 recurrence rate in adult GCT patients, with the most common sites being the pelvis and the liver.[8] For recurrent disease, effective debulking surgery combined with radiation and chemotherapy offers a high probability of survival.[9, 10] The prognosis for recurrent disease is determined by the age at recurrence and the treatment modality used. Patients under 50 at recurrence or those who receive single-modality treatment (surgery or chemotherapy alone) have a more than tenfold increased risk of cancer-related death compared to those who receive combination therapy.[10]

Extensive vascular reconstruction combined with debulking surgery for ovarian tumors is extremely rare. Finch et al. reported a case involving combined vena cava and aortic reconstructions in a 76-year-old patient with recurrent GCT.[11] Similarly combined resection of the liver and other viscera during debulking surgery for recurrent GCT is very rare, but successful resection provides an overall favorable outcome.[12] Given this rarity, our study aims to evaluate the outcomes of debulking surgery in patients with recurrent GCT that involves major abdominal vessels and the liver.

Methods

We serve as a reference center for primary and metastatic liver tumors. Between 2024 and 2025 we treated 3 cases of recurrent GCT. The details of the procedures are provided here in our case series. Since we are retrospectively presenting these cases, we did not require institutional review board approval for the ethical and scientific aspects of our study.

Study Parameters

We provide data about the patient's medical history, including when the index event occurred. The location of the recurrence and how it was diagnosed. Furthermore, we give the details of how we treated the patient. In addition, we provide the demographic details of the patients, including their age, information regarding pregnancies.

Laboratory data included the findings on the imaging procedures, and information regarding extreme laboratory findings is given. Furthermore, the macroscopic and macroscopic characteristics of the tumors are also summarized for each patient.

Statistical Analysis

All data are presented as descriptive data for patients. Age of the patients and duration between the index operation and the recurrences are expressed as a range. All statistical analyses were performed using Statistical software Package for Social Sciences version 24 (SPSS v24, Armonk, USA).

Results

Patient Demographics and Initial Surgeries

Table 1 summarizes the demographic, clinical, tumor, and laboratory characteristics of the three patients. Their ages ranged from 53 to 70 years. Two patients had a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), along with appendectomy and pelvic paraaortic lymph node dissection (PPaLND). The third patient underwent TAH, unilateral salpingo-oophorectomy (USO), PPaLND, and appendectomy. Notably, one patient had her initial operation at a different medical center. All the patients had adult-type GCT (Fig. 1A-C).

Recurrence and Subsequent Operations

The time from the initial operation to the first recurrence ranged from 6 to 26 years. The first recurrences were typically in the retroperitoneal space (two patients), with one patient's recurrence located in the left upper and lower quadrants. These were nearly always resected without needing to remove other organs. However, in Patient 3, a single recurrence occurred 26 years after the initial surgery

Table 1. Summary of the demographic and clinical characteristics of the Patients with GCT

Patient ID	Age	Duration and type of index operation	Chemotherapy	1st recurrence and timing	2nd recurrence and timing	3rd recurrence and timing	Elevation in tumor markers
Patient 1	70y	6 years TAH+BSO	None	Left UQ and Left LQ spaces 5 years after index operation	Right UQ and retroperitoneum 6 years after index operation (4 months after the first recurrence)	Pelvic 6 years after the index operation (5 months after the second recurrence)	None
Patient 2	53y	5 years TAH+ left USO	None	Retroperitoneal mass starting from SMA 5 years after the index operation	Right UQ and R LQ mass invading VCI. 5 years after the index operation (4 months after the first recurrence)	None	CEA was elevated since 1st year after the index operation and reduced after the operations for the two recurrences (currently 8 ng/ml)
Patient 3	68y	TAH+BSO PPaLND 26 yeas ago	Bleomycin, etoposide, and cisplatin	Retroperitoneal mass on the right extending to the right subdiaphragmatic region 26 years after the index operation	None	None	CA-125 was elevated since the recurrence, but is decreasing) (currently 38U/ml

*TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oopherectomy; USO: Unilateral salpingo-oopherectomy; PPaLND: Pelvic and para-aortic lymph node dissection; UQ: Upper quadrant; LQ: Lower quadrant; VCI: Vena cava inferior; CEA: Carcinoembryonic antigen; CA-125: Carbohydrate Antigen-125.

(Table 1). This mass extended from the right lower quadrant to the subdiaphragmatic space, necessitating a diaphragmatic resection (Fig. 2A-C).

Patients 1 and 2 experienced second recurrences in the retroperitoneal space and the right upper and lower quadrants, respectively, both diagnosed four months after the first recurrence. While the recurrent tumor in Patient 1 was resected without complications, Patient 2 required an excision of the anterior wall of the VCI, which was then reconstructed with a cryopreserved venous patch (Fig. 3A-C). Patient 3 had a third recurrence in the pelvis, diagnosed five months after the second, which was also successfully resected.

Tumor markers were elevated in two patients (Patients 2 and 3), and they reached peak levels before the recurrences. Carcinoembryonic antigen (CEA) and carbohydrate antigen-125 (CA-125) were the two markers that were elevated. Only one patient received adjuvant chemotherapy after the index operation. It included bleomycin, etoposide, and cisplatin.

Discussion

GCTs constitute 2-5% of all ovarian tumors, with the adult-type being classified as sex cord tumors of the ovaries. After initial surgery, the recurrence rate is 25%,[13] with one-third of recurrences happening within five years and nearly 20% within ten years.[13] Once recurrence occurs, the survival rate drops to less than 50%.[13]

Several factors predict a poor prognosis and a higher likelihood of recurrence, including the patient's age at initial diagnosis, the primary tumor's size, and specific histopathological characteristics like the mitotic index.[14] Leaving a residual tumor after the primary tumor's resection has been identified as the main determinant of a poor prognosis. The most common sites for recurrence are the pelvic cavity, liver, and lungs.[14]

The treatment of recurrence is a controversial topic; however, multimodal therapy, which includes effective debulking surgery, is typically recommended. Even with multimodality treatment, 60% of patients who experience an initial recurrence are reported to have a second or third recurrence.[15]

In our case series, two patients developed extra-pelvic recurrence, including one with a mass in the right retroperitoneal space. The third patient had a pelvic recurrence. All patients initially TAH + BSO. Our findings are consistent with previous case series.[14, 15] While we did not observe any extra-abdominal recurrences in our study, the pelvic recurrences were massive, requiring the concomitant resection of abdominal structures like the VCI in one patient.

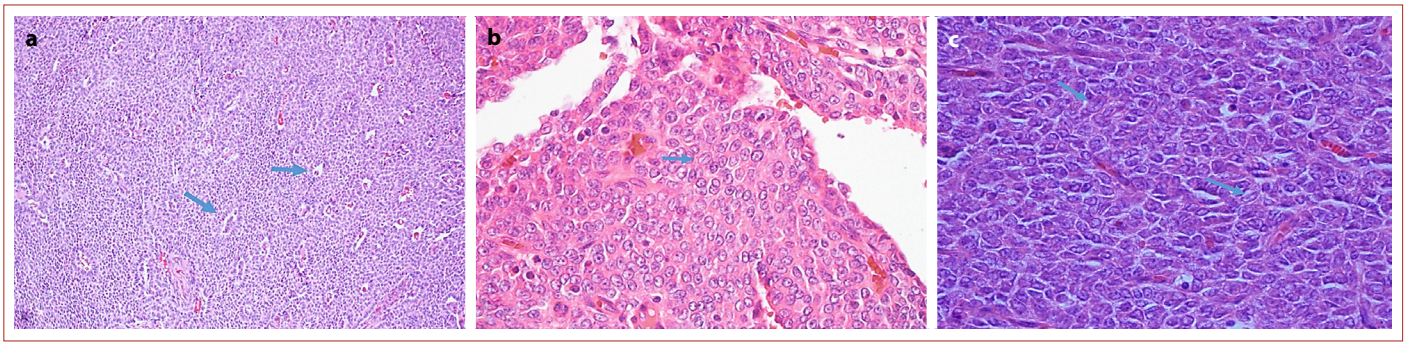

Figure 1. Summary of the different pathognomonic histological findings. **(a)** The most characteristic pattern of ovarian adult-type granulosa cell tumors is a microfollicular architecture, defined by the presence of Call-Exner bodies. These rosette-like structures resemble the Call-Exner bodies found in a Graafian follicle. Their centers are small, rounded spaces filled with eosinophilic cellular debris or hyaline basement membrane material, which are surrounded by numerous layers of granulosa cells. The image you're referring to is a hematoxylin and eosin (H&E) stain at 100x magnification, with arrows pointing to the characteristic pattern. **(b)** Coffee bean-like cells showing nuclear grooves (arrow), HE, 400X, **(c)** Grooved nuclei that look like coffee beans (arrows), HE, 200x.

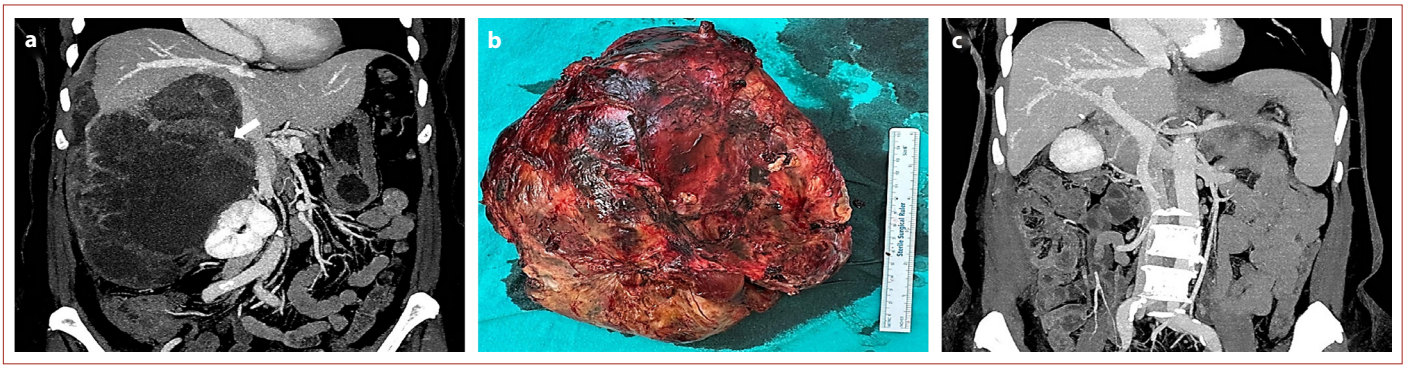

Figure 2. Summary of the large recurrent tumor. **(a)** The preoperative computerized tomography (CT) scan showing the large recurrent mass (arrow). **(b)** Shows the resection material intraoperatively. **(c)** Postoperative follow-up CT showing no recurrences.

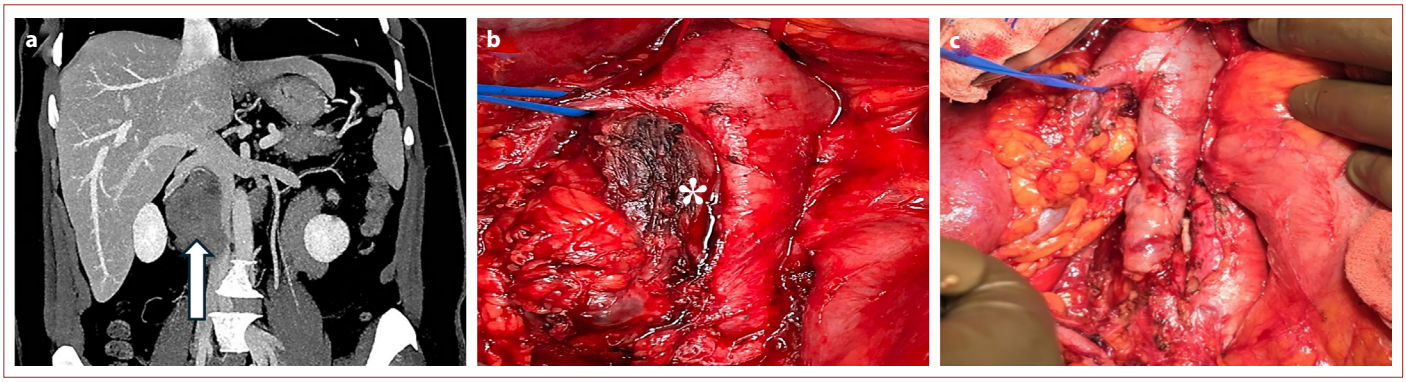

Figure 3. Summary of the patient with a recurrent tumor invading the infrarenal Vena Cava Inferior (IVC). **(a)** CT images of the recurrent mass (arrow). As shown, the mass is located inferior to the renal vein. **(b)** Intraoperative view showing the invasion of the anterior wall of the Vena Cava Inferior (asterisk). **(c)** The post-resection view showing the reconstructed IVC.

Complex oncovascular resections have been reported for epithelial ovarian tumors, and patient outcomes are usually favorable.[18] We performed a VCI anterior wall resection on one patient, and her follow-up has been uneventful, with no evidence of recurrence since the resection. Based on our data, oncovascular resections appear to have favorable outcomes.

The duration of progression-free survival is reported to determine the patient's prognosis.[11] However, our data shows that two-thirds of our patients had multiple recurrences that were successfully resected. Follow-up of these patients shows no evidence of recurrence. Similarly, Finch et al.[12] have reported a patient with multiple recurrences who was treated with repeated resections, including on-

covascular resections of the VCI. Therefore, repeated recurrences in GCT patients should not be considered an indication of an insufficient initial resection. We propose that the number of recurrences is not the primary concern, as long as each subsequent resection can be performed safely. This is further supported by Yumru Celiksoy et al.,[17] who demonstrated that different adjuvant therapies had no beneficial effect on disease-free survival in patients with recurrent adult GCTs.

Gurumuthy et al.[14] conducted a meta-analysis that evaluated five retrospective cohort studies, which included 535 women with GCT. Only one of these studies reported a beneficial effect of adjuvant chemotherapy, noting that it provided prolonged patient survival.[14] Also, other studies fail to show a survival benefit of adjuvant systemic chemotherapy following surgery for adult GCTs.[18-20] In our study, one patient who received adjuvant therapy following the index operation experienced a recurrence twenty-six years later. Therefore, adjuvant therapy can prolong the disease-free survival in selected patients.

Several markers, including inhibin, estradiol, and Müllerian-inhibiting substance, as well as histopathological parameters like Ki67, p53, and cluster of differentiation (CD) 56 expression, have been identified for the follow-up of GCTs.[21, 22] However, no single marker has definitive diagnostic or prognostic significance. In our study, we observed that CEA and CA-125 levels were elevated in our patients, with levels peaking before recurrence episodes.

The major limitation of our study is the small number of patients included. Nevertheless, we can still draw some conclusions from their clinical and tumor-related characteristics.

In conclusion, recurrent GCTs present a significant challenge from an oncologic surgery perspective. The number of recurrences is less important than the ability to achieve a complete resection of the recurrent tumor. The ability to perform a radical resection of recurrences, through surgery alone, appears to be the primary determinant of favorable patient survival. Furthermore, no tumor markers are currently reliable for the prognostication or diagnosis of these tumors.

Disclosures

Ethics Committee Approval: Ethics approval was not required for this retrospective study.

Informed Consent: Written and verbal informed consent was obtained from all patients.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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